DETAILED ACTION

1. Claims 27-32, 34-43 and 48-59 are all the pending claims.

2. Claims 27, 43 and 52 were amended and new claims 55-59 were added in the Response of 4/11/11 (and 4/15/11).

3. Claims 27-32, 34-43 and 48-59 are all the pending claims for this application.

4. Applicants re-instatement of cancelled claimed subject matter from original Claims 1, 2 and 17 filed 5/11/06 in the form of amending existing now claims raises new grounds for rejection. This Office Action is final.

Information Disclosure Statement

5. The IDS' of 3/2/11, 4/11/11 and 4/15/11 have been considered and entered. The initialed and signed 1449 forms are attached. The IDS filed 4/15/11 is a duplicate of the IDS filed 4/11/11, thus the reference has been stricken on the 1449 form of 4/15/11 pursuant to 37 CFR 1.97(c).

Withdrawal of Objections

Specification

6. The objection to the disclosure because of following informalities set forth in the Office Action of 3/23/10 is withdrawn.

Applicants' allegations on pp. 9-11 of the Response of 4/11/11 (and 4/15/11) have been considered and are found persuasive.

Sequence Listing/ Specification

New Matter

7. The objection to the amendment to the specification in the Response of 7/23/10 to change the sequence for the VH CDR3 domain from residues "Lys-Thr" to "Arg-Pro" as constituting new matter is withdrawn. Applicants revised Sequence Listing of 7/23/10 rectifies the absence of original written description support for the amendments to SEQ ID NOS: 3 and 4. Applicants have now provided any explanation why residues 106 and 107 have been corrected to amend the VH CDR3 domain from residues "Lys-Thr" to "Arg-Pro" in the Response of 4/11/11 (and 4/15/11) on p. 11 in addition to providing the statement of Dr. Hensel.

Specification

8. The amendment to the specification to enter the name and address of depository in addition to the date of hybridoma deposit has now been entered. Applicants' submission of a revised statement by Frank Hensel dated 4/21/11 overcomes the objection.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement

9. The rejection of Claims 27-32, 34-43 and 48-51 (and new Claims 52-54) under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for any antibody with binding specificity for "at least one of LDLs and oxidized LDL" and having the following structural properties: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or less than the full complement of VL CDR1-3 and VH CDR1-3 is withdrawn.

Applicants have established on the record with their comments on pp. 12-14 of the Response of 4/15/11 (and 4/15/11) and the exhibit C

Written Description/ New Matter

10. The rejection of Claims 43 and 52-54 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

The amendment to VH CDR3 of SEQ ID NO:3 having the following sequence: "Asp-Arg-Leu-Ala-Val-Ala-Gly-Arg-Pro-Phe-Asp- Tyr (CDR3) SEQ ID NO:3" is found to be supported by the revised statement of Dr. Hensel and Applicants comments on pp. 14-15 of the Response of 4/11/11(and 4/15/11).

Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. The provisional rejection of Claims 27-32, 34-43 and 48-59 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 73, 80, 81, 106-112, 115, 116 and 122-124 of copending Application No. 10/579,290 (US 20080108133) is maintained.

The rejection was set forth in the Office Action of 12/10/1o as follows:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims recite the same sequenced for the VH and VL domains of the claimed antibodies.
>
> This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants request on p. 15 of the Response of 4/11/11 (and 4/15/11) to hold the rejection in abeyance until all rejections are withdrawn is granted. The rejection is maintained.

New Grounds for Objection

Claim Objections

12. Claim 37 is objected to because of the following informalities:

a) Claim 37 recites "said heavy chain (VL) variable region" and should seemingly recite "said heavy chain (VH) variable region."

Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

13. Claims 27-32, 34-43 and 48-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is the examiner's position that the specification does not support a single variable domain or VH/VL pair derived from SEQ ID NO: 1 or 3 and binding different LDLs *and* oxLDLs (Claims 27 and 55); or a single variable domain or VH/VL pair derived from SEQ ID NO: 1 or 3 and wholly uncharacterized in their target antigen binding (Claims 42, 43, 54).

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised Mar 28, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: The working example in the specification discloses a single isolated human antibody, SAM-6 and sometimes called SAM-6.10, which binds LDL and oxidized LDL. At the time of filing, Applicant's specification did not reveal the structural identity of the antigen but generally characterized the antigen as LDL or oxidized LDL and the ability of the antibody to bind these LDL molecules was measured by an ELISA assay (page 14 of the specification). The specific antigen in the oxLDL, at least based on the commercial ELISA kit description, is actually for *apolipoprotein B* and *not* to any other components comprising the LDL or oxLDL. The sequence for the antibody (SAM-6 and/or SAM-6.10) is disclosed for VL and VH (SEQ ID NO:1 and 3, respectively). The antibody was shown to reduce LDL levels in vivo (Experiments 1 and 2, although no data is provided since the Figures which are discussed in the Specification are not present in the Application).

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the myriad antibody variants whether being a single variable domain or VH/VL pair derived from SEQ ID NO: 1 or 3 and binding different LDLs or oxLDLs (Claims 27 and 55); or a single variable domain or VH/VL pair derived from SEQ ID NO: 1 or 3 and wholly uncharacterized in their target antigen binding (Claims 42, 43, 54).

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with *correlation between structure and function* for the genus of the myriad antibody variants whether being a single variable domain or VH/VL pair derived from SEQ ID NO: 1 or 3 and binding different LDLs (Claims 27 and 55); or a single variable domain or VH/VL pair derived from SEQ ID NO: 1 or 3 and wholly uncharacterized in their target antigen (Claims 42, 43, 54).

d) Method of making the claimed invention: the specification teaches making a single human antibody from human lymphocyte sources and fusing into a trioma. The single SAM-6 antibody was selected and characterized based on its binding to oxLDL.

e) Level of skill and knowledge in the art: the selection of antibodies, cloning of antibody DNA, protein sequencing, and performing bioassays for identifying functional regions or functional properties was well established at the time of the invention.

f) Predictability in the Art: Adequate written description for an antibody appears to hinge upon whether the specification provides adequate written description for the antigen. While a specification may enable making a genus of antibodies, this does not necessarily place applicant in possession of the resultant antibodies (See *In re Kenneth Alonso* October (Fed. Cir. 2008) sustaining a lack of adequate written description rejection where "the specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies" where the specification does not characterize the

antigens to which the monoclonal antibodies must bind).

Here in the present case, Applicants are claiming myriad single domain antibodies having either a VH derived from SEQ ID NO:3 or a VL derived from SEQ ID NO:1; or antibodies having a VH derived from SEQ ID NO:3 and a VL derived from SEQ ID NO:1 which binds to any one of the genus of LDLs and oxLDLs (Generic Claims 27 and 55). Generic Claim 27 requires that one in the same antibody falling within this broad genus must bind LDLs and oxLDLs. Dependent Claim 28 requires that any one of amongst the myriad antibodies also binds LDL cholesterol and oxidized LDL cholesterol where the LDL cholesterol and oxidized LDL cholesterol may or may not share complementary carbohydrate structures. The examiner's search of what constitutes "LDLs" reveals that an LDL is one of five major groups of lipoproteins, which can be any one of in order of size, largest to smallest, chylomicrons, VLDL, IDL, LDL and HDL. The examiner submits that Applicants have not characterized the genus of antibodies having the ability to bind to all of the LDLs for the instant claim scope *but for* the apolipoprotein B found in the LDL. Thus, it is incorrect that the genus of antibodies binds any epitope anywhere located on just any LDL or any oxLDL because the only showing by Applicants is that the single species of SAM-6 antibody (SEQ ID NO: 1 and 3) binds apolipoprotein B.

Here in the present case, the single domain antibody of generic Claims 42, 43, 54 are not even required to have an intended antigen binding target. Thus, a single peptide sequence of the antibody is the only identifying characteristic. The ordinary artisan could not even begin to fathom what the genus of antibodies recognizes as a

common antigen. Accordingly, Applicants were not in possession at the time of filing for the genus of antigens much less the genus of antibodies recognizing those antigens.

Applicants have not characterized a representative species of antibody falling within the genus of antibodies meeting the instant claimed structure/function requirements to place Applicants in possession of the variant antibody species at the time of filing.

The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See *University of Rochester v. G.D. Searle & Co., Inc.,* 69 USPQ2d 1886,1895 (Fed. Cir. 2004). A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus of antibody that exhibit the functional property of binding the genus of LDLs and oxLDL in claims 27 and 55. A skilled artisan cannot visualize or recognize the identity of the members of the genus of antibody that have no defined antigen as in Claims 42, 43, 54.

For recent discussions of what constitutes written description support for a reasonable number of species see, for example, *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* (Fed. Cir. 2010) (en banc) stating:

> "a few broad principles hold across all cases"; "We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366-67 (Fed. Cir. 2006). Conversely, we have repeatedly stated that

> actual "possession" or reduction to practice outside of the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure, *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008), or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement, *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571-72 (Fed. Cir. 1997)."

> "For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.

Centocor Ortho Biotech Inc. v. Abbott Labs., No. 2010-1144 (Fed. Cir. 2/23/2011) where the Federal Circuit noted that the specification only included a mouse variable region and did not disclose a single human variable region. The court further stated that Centocor's mouse variable region was "very different" from the sequence of a human variable region like the one in Abbot's fully human antibody, and that the specification does not "disclose any relationship between the human TNF-α protein, the known mouse variable region that satisfies the critical claim limitations, and potential human variable regions that will satisfy the claim limitations." Therefore, the mouse variable region did not serve as a "stepping stone" to identifying a human variable region within the scope of the claims.

And in *Billups-Rothberg Inc. V. Assoc. Regional and Univ. Pathologists, Inc.* (Fed. Cir. 2011), Billups disclosed only the approximate location of the relevant mutation in a patent, a disclosure that it argued was sufficient to place the inventor in possession of the invention (which in this case included the step of detecting the mutation) when

combined with the knowledge that existed at the time of invention. The CAFC disagreed. "Given the lack of knowledge of sequences for the hemochromatosis gene and its mutations in the field, the limited extent and content of the prior art, and the immaturity and unpredictability of the science when the patent was filed, Billups cannot satisfy the written description requirement merely through references to later-acquired knowledge."

There is insufficient guidance and direction as to the written description of the claimed antibody, as broadly encompassed by the claimed invention. Given the well-known high level of polymorphism of antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies and the unlimited number of antibodies encompassed by the claimed invention; one of skill in the art would conclude that applicant was not in possession of the functional attributes of a representative number of species possessed by the members of the genera of an antibody which binds to any LDL and oxLDL much less LDL cholesterol and oxLDL cholesterol. Still further, the skilled artisan could reasonably conclude that Applicants were not in possession of an antibody having a VH or VL domain of generic Claims 42, 43, 54 that are not even required to have an intended antigen binding target.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Giles-Komar et al. (WO200212502; filed 8/7/01).

Claim 43 is interpreted as being drawn to any antibody fragment binding to any antigen so long as the fragment comprises either of a CDR1 or CDR2 sequence and having the same sequence as CDR1 or CDR2 of SEQ ID NO:3.

Giles-Komar teaches an antibody fragment comprising the following sequence:

```
     SQ   Sequence 115 AA;
   Query Match             92.0%;  Score 528;  DB 1;  Length 115;
   Best Local Similarity   92.7%;  Pred. No. 6e-42;
   Matches  102;  Conservative    2;  Mismatches    6;  Indels    0;  Gaps
0;
 Qy          1 QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVREAPGKGLEWVAVISYDGSNKYY
60
               ||||||||||||||||||||||||||||||||||||:||||||||||||||||||||
 Db          1 QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYY
60
 Qy         61 ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRLAVAGKTFDY 110
               |||||||||||||||||||||||||||||||||||||   ||  : |
 Db         61 ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGISAGGNYYY 110
```

The sequence comprises a domain having the same sequence as the CDR1 sequence of SEQ ID NO:3 and a domain having the same sequence as the CDR2

sequence of SEQ ID NO:3. The antibody fragment of Giles-Komar is considered to broadly read on Claim 43.

Conclusion

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Art Unit 1643
Primary Examiner